IMMUNOLOGY

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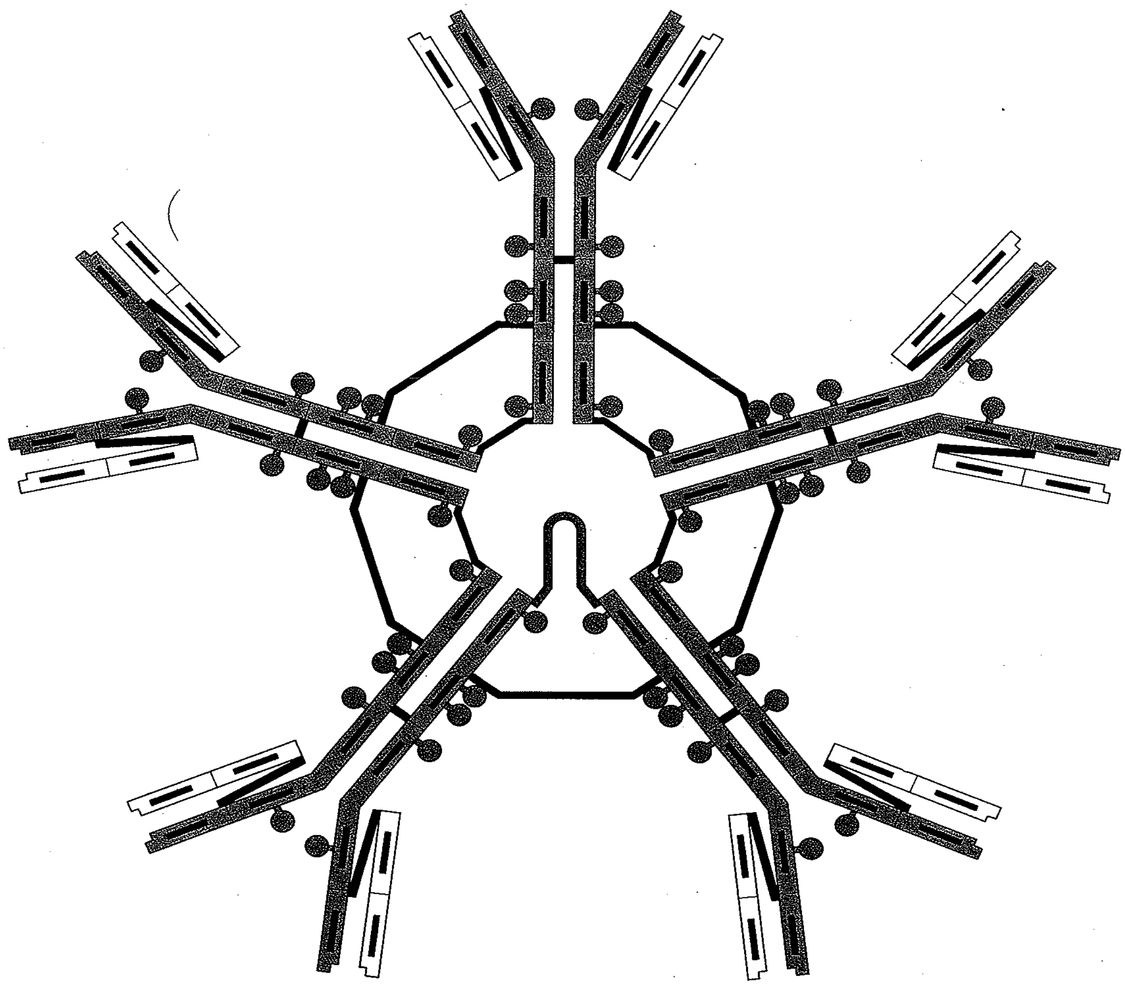

IMMUNOLOGY

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5 Antibody Structure and Function

The immunoglobulins, or antibodies are a group of glycoproteins present in the serum and tissue fluids of all mammals. Their production is induced when the host's lymphoid system comes into contact with immunogenic foreign molecules (antigens) and they bind specifically to the antigen which induced their formation. They are therefore an element of the adaptive immune system.

present nomenclature	shorthand	previous nomenclature
immunoglobulin G	IgG	γG globulin 7S γ-globulin
immunoglobulin A	IgA	γA globulin β_2A-globulin
immunoglobulin M	IgM	γM globulin 19S γ-globulin $\gamma_{\text{-IM}}$ γ-macroglobulin
immunoglobulin D	IgD	γ-SJ
immunoglobulin E	IgE	Reagin, IgND

Fig. 5.1 Nomenclature of the five classes of immunoglobulin molecule. These are the five classes recognized in most higher mammals.

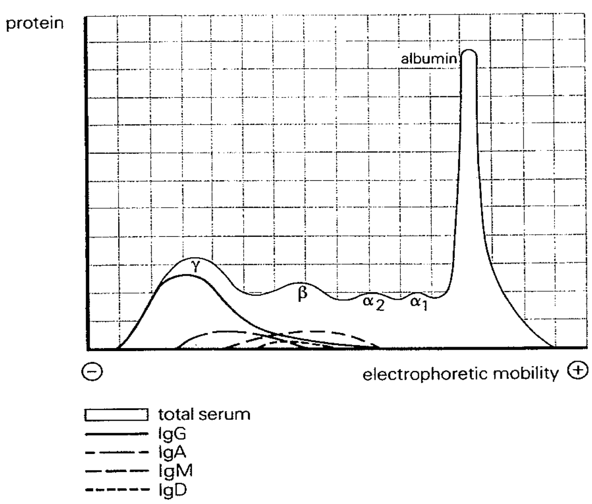

Fig. 5.2 Immunoelectrophoresis of human serum showing the distribution of the four major immunoglobulin classes. Serum proteins are separated according to their charge in an electric field, and classified as α_1, α_2, β, and γ, depending on their mobility. (The IgE class has a similar mobility to IgD but cannot be represented quantitatively because of its low level in serum.) IgG exhibits most charge heterogeneity, the other classes having a more restricted mobility in the slow β and fast γ regions. These fractions suffer marked depletion following absorption with antigen suggesting a role for them in the immune response.

THE FIVE IMMUNOGLOBULIN CLASSES

Five distinct classes of immunoglobulin molecule are recognized in most higher mammals, namely IgG, IgA, IgM, IgD and IgE (Fig. 5.1). These differ from each other in size, charge, amino acid composition and carbohydrate content. In addition to the differences between classes the immunoglobulins within each class are also very heterogeneous. Electrophoretically the immunoglobulins show a unique range of heterogeneity which extends from the γ to the α fractions of normal serum. In general it is the IgG class which exhibits most charge heterogeneity, the other classes having a more restricted mobility in the slow β and fast γ regions (Fig. 5.2). The basic four chain polypeptide structure of the immunoglobulin molecule is represented in figure 5.3.

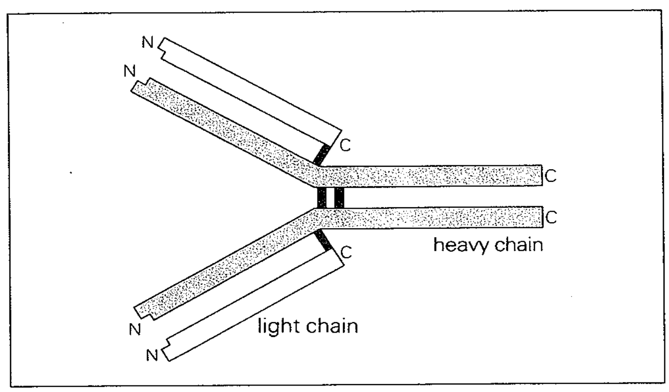

Fig. 5.3 The basic immunoglobulin structure. The unit consists of two identical light polypeptide chains and two identical heavy polypeptide chains linked together by disulphide bonds (red). Note the position of the amino (N) and carboxy (C) terminal ends of the peptide chains.

ANTIBODY FUNCTION

Essentially each immunoglobulin molecule is bifunctional; one region of the molecule is concerned with binding to antigen while a different region mediates binding of the immunoglobulin to host tissues, including various cells of the immune system, some phagocytic cells, and the first component (C1q) of the classical complement system.

The immunoglobulins also display a complex pattern of interactions with various cell types and some of these are tabulated in figure 5.17. Some of this data is still controversial, particularly that relating to the interactions with lymphocytes, and further clarification may follow from improved definition of cell subpopulations.

STRUCTURE IN RELATION TO FUNCTION

The plant proteinase papain cleaves the IgG molecule in the hinge region between the Cγ1 and Cγ2 domains to give two identical Fab fragments and one Fc fragment. The fragments generated by papain have been of enormous value in structure/function studies on the antibody molecule. It was noted that the Fab region is concerned with binding to antigen while the Fc region mediates effector functions such as complement fixation, monocyte binding and placental transmission.

Another useful enzyme for such studies is pepsin which generates two major fragments: the $F(ab')_2$ fragment which broadly encompasses the two Fab regions linked by the hinge region, and the pFc' fragment, which corresponds to the Cγ3 domain of the molecule. Papain also generates, after prolonged digestion periods, a degraded fragment of the Cγ3 region which is called the Fc' fragment. Some of these major points of enzymic cleavage are shown in figure 5.18. Many other enzymes are known to cleave the immunoglobulin molecule. Brief trypsin digestion of acid-treated Fc fragment yields the Cγ2 domain, and isolation of this fragment has permitted extensive structural and functional comparisons with other subfragments such as pFc'.

The recognition of immunoglobulin domains as functional subunits led Edelman in 1970 to suggest that each had evolved to subserve a specific function. There was already clear evidence that the V_H and V_L domains interact to form the antigen binding surfaces of the antibody molecule, and subsequent crystallographic work (see later) has amply confirmed this prediction. Edelman suggested that the other domains would be shown to mediate the other (effector) functions of immunoglobulin. Precise structural location of these other sites has still to be achieved but there is good evidence that the C1q component of complement interacts with the Cγ2 domain (in the case of IgG) and that a site controlling the rate of catabolism of the whole molecule is in the same domain.

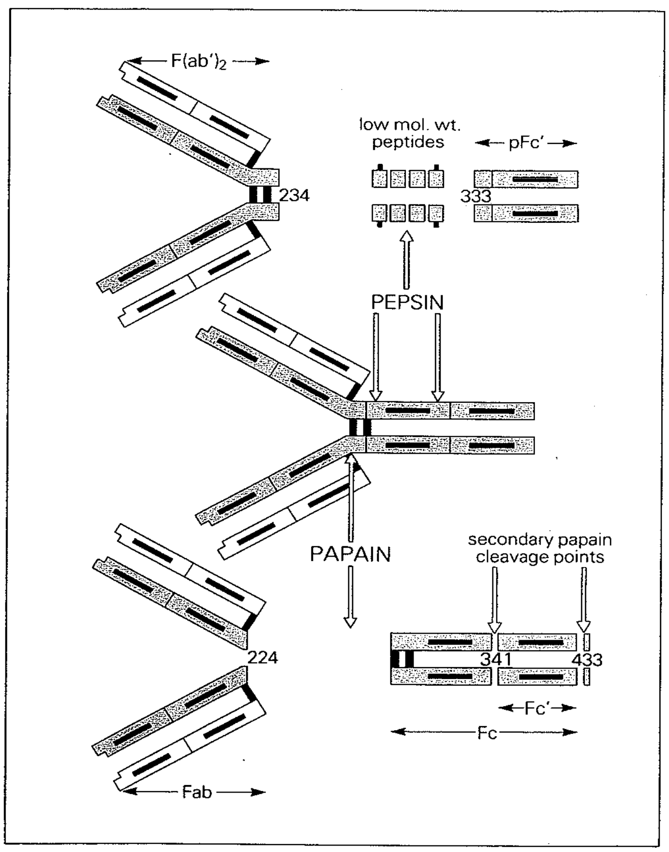

Fig. 5.18 Enzymic cleavage of human IgG1. Pepsin cleaves the heavy chain at the amino acid residues, 234 and 333, to yield the $F(ab')_2$ and pFc' fragments. Further action reduces the central fragment to low molecular weight peptides. Papain splits the molecule in the hinge region (at residue 224) yielding two Fab fragments and the Fc fragment. Secondary action on the Fc fragment at residues 341 and 433 gives rise to Fc'.

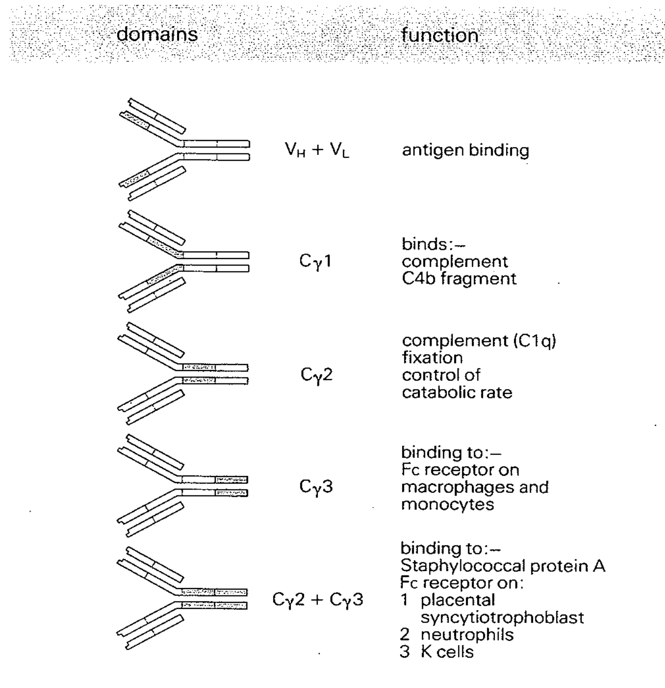

Fig. 5.19 Functions of IgG domains. The relevant domains are shown shaded, together with the functions they perform.

There is much data to suggest that interactions with macrophages and monocytes occur through a site in the Cγ3 domain but an adjunctive function for the Cγ2 domain in such reactions appears likely. Similarly there is evidence that interaction with other cell structures either occurs through sites spanning the two Fc domains (Cγ2 + Cγ3) or requires some synergistic activity between these two domains. The functions performed by domains of the IgG antibody are summarized in figure 5.19.